REMARKS

Claims 31-53 presently appear in this case. No claims have been allowed. The official action of October 24, 2000, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to methods for antitumor therapy involving administering to a subject in need of such treatment a therapeutically effective amount of a chemotherapeutic drug and an immunostimulating cytokine. The cytokine is encapsulated in multilamellar liposomes (MLV) and in one embodiment the chemotherapeutic drug is also separately encapsulated in liposomes. The administration produces a greater therapeutic effect than the sum of the effects produced by administration of the chemotherapeutic drug alone or the immunostimulating cytokine alone, either encapsulated or not.

The examiner states that the use of the trademarks DOXIL® and STEALTH® has been noted, stating that they should be capitalized wherever they appear and be accompanied by the generic terminology at the first instance.

The specification has now been amended to provide the term "STEALTH" in all capital letters. DOXIL is already capitalized. Generic terminology for DOXIL has now been added to page 2, line 22, in order to specify that it is "a

polyethylene glycol-coated liposomal doxorubicin." This is the commonly used terminology relating to DOXIL and is supported by the specification at page 7, lines 19-21, where it states that DOXIL is "a stable formulation of adriamycin in STEALTH® liposomes". Page 3, line 21, indicates that STEALTH liposomes are PEGylated SUV liposomes. That "PEGylated" means polyethylene glycol-coated is evident from page 4, lines 22-31, for example. Accordingly, this terminology with respect to DOXIL contains no new matter. With respect to STEALTH, note that generic terminology is already present at page 3, lines 20-22, the first place it appears, which states that STEALTH® is PEGylated SUV liposomes. Accordingly, this requirement has now been complied with.

The examiner states that the first line of the specification should be amended to indicate that the present application is a 371 of the earlier filed PCT application.

The present specification has now been amended in order to insert this reference.

Claims 1-24 have been rejected under 35 USC 112, second paragraph, as being indefinite. The examiner states that in claims 1 and 14 applicant needs to specify clearly what is being administered, i.e., whether the drugs encapsulated together or separately in different liposomes.

Claims 1 and 14 have now been deleted and new independent claims 31 and 42 have been added. In claim 31, only the cytokine is specified as being encapsulated in liposomes and therefore this objection is not applicable. With respect to claim 42, it is now stated that the cytokine is separately encapsulated, thus clarifying this point.

The examiner states that in claims 2, 15 and 24 applicant needs to further define what "individually" means.

The term "individually" has now been replaced by the term "alone" to better define that the sum of the effects relates to the effect obtained when each component is administered without the other.

The examiner states that in claims 6, 12, 16 and 26 the Markush groups should be correctly phrased.

The new claims now use the correct phraseology for Markush language, thus obviating this part of the rejection.

The examiner states that claim 5 recites the limitation "vesicle" in line 1 without antecedent basis.

Claim 5 has now been deleted and the new set of claims does not use the term "vesicle".

The examiner states that in claims 13 and 22 the use of the word "follows" does not clearly indicate the amount of time between administrations.

The term "follows" in new claims 38 and 53 (corresponding to original claims 13 and 22) is now used in association with the term "time interval". This latter term is defined in the claim as follows:

> the time interval ... is such that the combined therapeutic effect of said administrations is greater than a sum of the therapeutic effects produced by administration of the chemotherapeutic drug alone and by administration of said immunostimulating cytokine alone.

This is supported on page 11, lines 15-19, of the specification. Accordingly, this part of the objection has now been obviated.

The examiner states that the term "about 1-10" in claims 3, 5, 14 and 25 is a relative term which renders the claim indefinite. The examiner then states, however, that the amount of mole percent should be specified using either a range or a definite relative term such as, for example, "about". This part of the rejection is respectfully traversed.

If the examiner concedes that "about" is a definite relative term, then it is not understood why the term "about 1-10" is considered indefinite. Furthermore, the MPEP at §2173.05(b)(A) indicates that the term "about" is clear but flexible and should be acceptable except in cases where there is close prior art. Here, there is no close prior art over

which the range is intended to define. Furthermore, the examiner has conceded that the term "about" is "a definite relative term". Accordingly, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner states that the term "analog" in claims 8 and 19 is a relative term which renders the claim indefinite.

This term has now been deleted, thus obviating this part of the rejection.

Claims 9, 18 and 28 have been rejected under 35 USC 112, second paragraph, because the use of the trademark DOXIL® is improper.

The trademark DOXIL® has now been replaced with the commonly used terminology of DOXIL®, being "polyethylene glycol-coated liposomal doxorubicin". This term has now been inserted into the specification at page 2 as discussed hereinabove and supports use of this term in the claim. Accordingly, this rejection has now been obviated.

Claims 1, 2, 10, 11, 13, 23, 24, 29 and 30 have been rejected under 35 USC 102(a) as being anticipated by Kedar (1997). The examiner states that Kedar (1997) discloses a highly efficacious eradication of tumors comprising a liposome encapsulated chemotherapeutic drug and liposome encapsulated IL-2. This rejection is respectfully traversed.

While this publication discusses the advantages of using liposomal IL-2 in combination with a chemotherapeutic drug for the treatment of cancer, it does not teach or suggest the preferable use of multilamellar liposomes (MLV) for encapsulating IL-2 over other types of liposomes (e.g., SSL), as disclosed and claimed herein. The particular use of MLV avoids anticipation. Furthermore, the present specification establishes that the effect obtained by the specific treatment including liposomal cytokine in combination with chemotherapeutic drug is synergistic. This synergistic effect rebuts any *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 2, 4, 6, 7, 9-13, 23, 24, and 26-30 have been rejected under 35 USC 102(b) as being anticipated by Fondy. The examiner states that Fondy discloses IL-2 formulated with cytochalasin using liposomes, which can be further administered with doxorubicin with or without liposomes. This rejection is respectfully traversed.

Fondy describes the use of IL-2 to eliminate the immunosuppression produced by cytochalasins. It does not teach or suggest the encapsulation of IL-2 in liposomes. Reference should be made to pages 20-21 of Fondy which

specifically discuss the administration of IL-2. This section does not teach or suggest administration of IL-2 in liposomes.

There are advantages in providing a subject with cytokines in liposomes. Attached hereto are copies of the following two of several recent publications discussing the advantages of using liposomal IL-2 over using free IL-2:

> Kedar et al, "Delivery of Cytokines by Liposomes: Hematopoietic and Immunomodulatory Activity of Interleukin-2 Encapsulated in Conventional Liposomes and in Long-Circulating Liposomes", J. Immunotherapy, 23(1):131-145 (2000); and
>
> Kedar et al, "Delivery of cytokines by liposomes: a means of improving their immunomodulatory and antitumor activity", in "The Biotechnology of Cancers: From Immunotherapy to Gene Therapy", S. Chouaib, ed. INSERM-PNAS, pages 333-362 (1998).

In addition to the above, it should be noted that even if reference to liposomal IL-2 was made in this publication, which is not the case, this publication does not teach or suggest the preferable type of liposomes used, being the MLV liposomes. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 1-7, 9-18 and 20-30 have been rejected under 35 USC 102(b) as being anticipated by Kedar et al (1993). The examiner states that Kedar discloses an antitumor therapy using encapsulated IL-2 and doxorubicin using cholesterol and PEG1900-DSPE. This rejection is respectfully traversed.

First of all, it is not clear why the left-hand column of the PTO-892 was checked off and copies of the references were not furnished. References such as this were not previously cited of record and must be provided to applicants. Furthermore, it is not entirely clear to which publication of Kedar et al the examiner refers, as there seems to be a mistake in the reference's details in the list of citations. Attached hereto is a copy of the publication which the applicant believes the examiner is referring to, i.e., Kedar et al "Delivery of Cytokines and Anti-Cancer Drugs by Liposomes and Immunoliposomes", J. Imunother., 14:360 (1993). This publication does not teach or suggest the use of MLV encapsulated cytokines nor does it teach or suggest the synergistic effect obtained from treatment with a chemotherapeutic drug followed by treatment with liposomal cytokines. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged. If the examiner is relying on another reference, it is requested that a copy be provided to applicant and any further rejection based thereon be non-final.

Claims 1-7, 9, 10, 12-18, 20 and 22-29 have been rejected under 35 USC 102(a) as being anticipated by ten Hagen. The examiner states that ten Hagen discloses an antitumor therapy using STEALTH liposome-encapsulated

doxorubicin and STEALTH liposome-encapsulated TNF-α. This rejection is respectfully traversed.

It should be noted that TNF-α has a broad range of biological properties/effects outside the immunomodulator field and, thus, is not considered a typical immunomodulator. Unlike IL-2, which boosts the immune system against the tumor, TNF-α mainly exerts a direct effect on the tumor by killing the tumor cells (apoptotic death) and by blocking blood supply to the tumor tissue. Further, it should be noted that TNF-α, unlike IL-2, is not approved for systemic administration to humans because of its high toxicity.

Furthermore, it should be noted that the liposomes employed by ten Hagen are STEALTH liposomes which are different from the MLVs employed by the present invention for encapsulating the cytokines. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 8 and 19 have been rejected under 35 USC 103(a) as being unpatentable over Kedar et al (1993) in view of Poirot and the Merck Index. The examiner states that, while Kedar does not disclose the use of camptothecin as the chemotherapeutic agent, the Merck Index discloses that camptothecin exhibits antitumor activity and Poirot discloses the use of liposome-encapsulated camptothecin and cytotoxicity assays of KB cells. The examiner states that one of ordinary

skill would have been motivated to use camptothecin as a choice of chemotherapeutic agent in the liposome-encapsulated IL-2, chemotherapeutic agent used by Kedar et al, since liposome-encapsulated camptothecin was known as an effective cytotoxin against KB cells and was known as an antitumor agent. This rejection is respectfully traversed.

No combination of references cited by the examiner suggests the therapeutic advantage of using MLV encapsulated cytokines over other types of liposomes. The mere fact that it is possible to encapsulate cytokines and chemotherapeutic drugs and delivery systems such as liposomes, does not make obvious the synergistic effect obtained as disclosed in the present application and required by the present claims. Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 8 and 19 have been rejected under 35 USC 103(a) as unpatentable over Kedar et al (1993) in view of Burke. The examiner states that one of ordinary skill in the art would have been motivated to use camptothecin or the camptothecin-like drugs as a choice of chemotherapeutic agent and the liposome-encapsulated IL-2, chemotherapeutic agent used by Kedar, since liposome-encapsulated camptothecin and the camptothecin-like drugs were known as an antitumor agent

from the disclosure of Burke. This rejection is respectfully traversed.

As discussed hereinabove with respect to the previous rejection, combining the two publications would not have rendered the use of MLV cytokines obvious. Furthermore, the combination of the two publications does not teach or suggest the synergistic effect obtained by using encapsulated cytokine in combination with chemotherapeutic drugs (either encapsulated or free). Accordingly, reconsideration and withdrawal of this rejection are also respectfully urged.

Claims 8 and 19 have been rejected under 35 USC 103(a) as being unpatentable over Kedar et al (1993) in view of Chow. The examiner states that one of ordinary skill in the art would have been motivated to use camptothecin or the camptothecin analog as a choice of chemotherapeutic agent in the liposome-encapsulated IL-2, chemotherapeutic agent used by Kedar, since liposome-encapsulated camptothecin and 9-nitro-camptothecin were known as effective antitumor agents from Chow. This rejection is respectfully traversed.

Again here, as discussed above with respect to the previous two rejections, it must be understood that the fact that it is known that one can possibly encapsulate a chemotherapeutic drug in a cytokine and liposomes, does not make the specific treatment of the present invention, i.e.,

treatment with MLV-cytokines in combination with a chemotherapeutic drug, which results in a synergistic effect, obvious. Reconsideration and withdrawal of this rejection are therefore also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record. Reconsideration and allowance are therefore earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

A paragraph has been inserted between lines 2 and 5 on page 1.

The paragraph beginning at page 2, line 19, has been amended as follows:

--The chemotherapeutic drug is preferably selected from cis-platin, a chemotherapeutic anthraquinone, and a topoisomerase I inhibitor, such as camptothecin or a camptothecin analog. More preferably, the drug is adriamycin (doxorubicin), in which case the liposome-encapsulated form of the drug is preferably DOXIL®, a polyethylene glycol-coated liposomal doxorubicin.--

The paragraph beginning at page 3, line 19, has been amended as follows:

--Figure 2 shows the survival rate of BALB/c mice injected intravenously with $5x10^5$ M109 tumor cells and subsequently treated with DOXIL® (at day 7), alone or in combination with intravenous IL-2 in ~~Stealth~~STEALTH® PEGylated SUV liposomes (at days 11, 14, and 17), or with liposomal IL-2 alone (at days 11, 14, and 17).--

The paragraph beginning at page 4, line 22, has been amended as follows:

Corp. (Emeryville, CA) as a formulation of doxorubicin hydrochloride and lactose.--

In the claims:

Claims 1-30 have been cancelled.

New claims 31-53 have been added.

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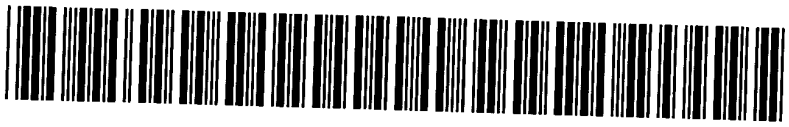

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